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(54) PROLONGED RELEASE LOZENGES

(71) I, HANS LOWEY of 7 Deerfield Lane, Mamaroneck, New York, United States of America a citizen of the United States of America, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to prolonged release lozenges, more particularly to compressed lozenges and tablets are described which have a regular and prolonged release pattern for a medicament or active ingredient incorporated therein and wherein the lozenge or tablet is composed of a carrier of hydroxypropyl methylcellulose with or without a proportion of sodium carboxymethylcellulose and with or without a small proportion up to 20% by weight of ethylcellulose and incorporated therein a medicament or active ingredient.

Hydroxypropyl methylcellulose is known and commercially available as Methocel (Dow Chemical Co.) (the word "Methocel" is a Registered Trade Mark) and a premium grade known as Methocel 60 H.G.-50 viscosity is used herein. Sodium carboxymethylcellulose is also well known. Methocel has been considered as lacking in the most desirable properties for making compressed long lasting troches and as a result dry skim milk powder combined with a binder such as Guar gum has been substituted (U.S. Patent No. 3,590,117). Carboxypolymethylene and sodium caseinate have also been used for the same purpose (U.S. Patent No. 3,594,467). It is also known that sublingual lozenges and tablets intended to be swallowed have been made with various active agents and carriers, but where prolonged action is desired and a regular rate of release is needed no fully satisfactory carrier has heretofore been produced with a consistent release pattern as a result of which the art is still seeking a solution to this problem.

According to the present invention it has been discovered that the disadvantages of prior products containing Methocel as described in U.S. Patent No. 3,594,467 can be overcome by special treatment thereof under controlled temperature, humidity and time conditions and thus the inherently desirable properties of Methocel can be taken advantage of in a sustained release compressed lozenge or tablet. The present invention therefore subjects hydroxypropyl methylcellulose (the chemical name of Methocel) to special temperature, moisture and time processing conditions thereby producing a modified carrier material having about the same or slightly lower molecular weight than the untreated form as determined by light scattering photometry and which has been found to be highly satisfactory and unique in that it is bland, non-irritating, substantially neutral and adherent, and gives a regular or constant rate of minimal effective release of an active ingredient incorporated therein and an emollient and protective action on tissue lesions. Thus, it is not necessary to go to other materials as the prior art has done.

The hydroxypropyl methylcellulose used as the starting material for the present invention is known as Methocel 60 H.G.-50 viscosity which is a premium grade found best for pharmaceutical products and this hydroxypropyl methylcellulose can be optionally combined with a small proportion of sodium carboxy - methylcellulose up to about 15% of the weight of the mixture. This is done by mixing these two materials in powder form prior to subjecting them to the hereinafter described processing steps. Alternatively, the products produced in accordance with the invention beneficially contain about 0 to 20% by weight of ethyl cellulose and this most preferred form of the invention contains all three materials. These materials are thoroughly mixed and sifted when necessary and then processed through the equipment hereinafter described under the conditions set forth and after the materials are processed as described, an active ingredient of suitable amount to provide an effective unit dose per lozenge or tablet is incorporated therein and which can be of any type of material which

acts through the buccal tissues of the mouth to transmit the active ingredient directly into the blood stream thus by-passing the gastric and intestinal fluids which often have an adverse inactivating or destructive action on many active ingredients unless they are specially protected against such fluids as by means of an enteric coating. Preferably the carrier and the active ingredient constitute at least 80 to 90% of the weight of the lozenge. Representative active ingredients are conventional antacids, anti-inflammatory steroids, vasodilating agents, anti-histamines, laxatives, decongestants and vitamins. Particular examples of the active ingredient are gastric mucin, aluminium hydroxide, magnesium trisilicate, nitroglycerin, amyl nitrite, 1 - ascorbic acid, chlorpheniramine maleate, benzocaine, phenolphthalein and dextrose and mixtures thereof. However, it is to be understood that the invention is not limited to sublingual lozenges as it is also applicable to compressed tablets which are intended to be swallowed and which nevertheless give slow and regular release of active ingredient in the general intestinal tract. The hydroxypropyl methylcellulose alone or with a small proportion such as 5 to 15% of sodium carboxymethylcellulose and with 0 to 20% of ethylcellulose by weight forms what is herein called a long acting slow dissolving oral carrier and this carrier is of such nature that it has a protective, demulcent and buffering effect on lesions in the mouth or other locations in the body and causes the active ingredient to exert its optimum action so that full advantage can be taken of the entire or substantially the entire amount of active ingredient present. This unexpectedly high degree of efficiency is a particular advantage of the invention.

The procedure is carried out by introducing the hydroxypropyl methylcellulose or a mixture of the hydroxypropyl methylcellulose and sodium carboxymethylcellulose or mixture of both with ethyl cellulose into an oven chamber having an exhaust aperture which is at that time in closed or shut position and which chamber is provided with a heating unit and a forced air blower which is inoperative at this stage of the procedure in that the heat and forced air are only applied at a subsequent stage. The material to be processed is placed in thin layers (not more than 1/4" thick) on trays of the oven chamber which are lined with heat-resistant parchment paper and the trays are placed on racks in the oven chamber using only alternate shelves thereby providing a predetermined amount of spacing between the layers of material being treated. There is then placed within the oven chamber a humidifier equipped with a humidistat which is pre-set to maintain humidity in the oven chamber at 85—90%, the humidifier being filled with sufficient distilled or deionized water to last for 24 to 36 hours. The humidifier is now activated and the oven chamber is closed and the process is allowed to proceed under the 85—90% humidity for a minimum of 24 hours. This minimum time is of critical significance and should not be appreciably less, but humidification may be continued for up to 36 hours or even longer if desired, although there is no special advantage in exceeding 36 hours and unduly extended times are apt to be uneconomical. Subsequent to the 24-hour minimum period just referred to, the humidifier is removed from the oven chamber, the exhaust aperture opened by manipulation of the usual valve or closure thereof and the forced air blower is activated thereby applying heat at a controlled temperature in the range of 110° to 120°F (43° to 49°C) and at the end of 12 hours the moisture content of the treated material is checked by removing a sample and the moisture content must not be outside the range of 2 to 2 1/2% in terms of added weight of the material undergoing processing. This added moisture content is equivalent to 4 to 4 1/2% as determined by a standard moisture determination apparatus. The 12-hour period just referred to is approximate as the duration of the period may vary somewhat above or below 12 hours, but it has been found in practice that the period should best be approximately 12 hours. The attainment of the specified additional moisture percentage is important and considered critical to the success of the invention.

When the required added moisture content is achieved, and referring now to the processing of hydroxypropyl methylcellulose alone, the treated material is removed from the oven and passed through a No. 2 stainless steel screen employing a Fitzpatrick Comminuter having its knives directed forwardly and operating at medium speed. In the case of the treatment of a mixture of hydroxypropyl methylcellulose and sodium carboxymethylcellulose the comminution step is omitted and the heat is applied until the moisture content is between 0.7 and 1.0% by weight as determined by the usual moisture determination apparatus. Since the material is free-flowing and powdery, no further operation is required thereon. The same is also true when ethyl cellulose is present.

By way of example, in making up tablets or lozenges containing an orally administrable buccally absorbable active component such as one of the known antacids, the treated oral carrier material is thoroughly intermixed with the antacid such as aluminum hydroxide gel or such gel with magnesium trisilicate which is also in powdered form and any other needed ingredients which are conven-

tional in tablet or lozenge making such as magnesium stearate, lactose, starch and, in general, binders, fillers and disintegrating agents, when desired. The complete mixture—in an amount sufficient to make a batch of tablets or lozenges, such as 50,000, of which each contains an effective amount of active ingredient—is then subjected to tableting in conventional tableting machines at for example pressures of 7 to 13 kg per sq. inch and because of the use of the specially processed carrier material in the production of the lozenges and tablets, a product is obtained which has a predetermined set of properties such as prolonged solubility and a delayed release pattern so that the antacid or other active medicinal agent or ingredient is available over a period of 1 to 8 hours or more depending on the tablet hardness and the particular carrier mixture. In this way it is possible to produce sustained or slow release lozenges or tablets in relatively simple economical fashion as contrasted with the more elaborate and more complex materials and procedures heretofore employed or proposed.

The humidifier employed is Arvin Model 50 H 42 (Sears-Roebuck)—10 gallon capacity having low and high air speeds and the humidistat is provided with 9 settings for moisture control. In the present invention the humidistat is set to position 7 which maintains 85 to 90% humidity in the oven chamber per 250 cubic feet of air and a temperature of approximately 75°F (24°C). It is understood that the invention is not limited to the use of this particular humidifier or equipment.

The invention is further illustrated by the following examples 1 to 6 and 9: wherein the carrier is initially treated under controlled temperature, humidity and time conditions i.e. a temperature between 110 and 120°F at a humidity of 85 to 90% for a minimum of 24 hours.

EXAMPLE I

Demulcent and Adsorbent

A demulcent and adsorbent lozenge was prepared from the following ingredients in the following relative proportions.

	Ingredients	mg/tablet
1	Methocel 60 HG.—50 viscosity	232
2	Gastric mucin	25
3	Aluminum hydroxide gel dried granular	250
4	Magnesium trisilicate granular	250
5	Methyl paraben U.S.P.	0.8
6	Propyl paraben U.S.P.	0.08
7	Felcofix cherry flavor No. 1265	16
8	Syloid 244 (Silica aerogel)	5
9	Carbowax 6000W*	6.81
10	Stearic acid	8.0

*The word "Carbowax" is a Registered Trade Mark.

Using the foregoing ingredients, a batch weighing 793.69 g was prepared by weighing out ingredients 1—4, screening ingredients 5—10 and mixing and blending all ingredients for 20 minutes following which they were subjected to compression in a tableting machine having a 1/2" die size and a 1/2" punch to make tablets with an average weight of 0.794 g and a thickness of 0.210" ± 0.01". The hardness of the tablet was 11—13 kg/square inch.

EXAMPLE II

Analgesic

	Ingredients	mg/tablet
1	Aspirin powder U.S.P.	525.0
2	Methocel 60 HG.—50 viscosity	325.5
3	Glycine	45.0
4	Syloid 244 (Silica aerogel)	4.5

Ingredients 1, 2 and 3 are mixed in a bowl into which ingredient 4 is added after screening and the whole blended for 20 minutes and compressed in the manner described in Example I. Each tablet weighed .9 g.

EXAMPLE III

Antihistamine

	Ingredients	mg/tablet
1	Chlorpheniramine maleate U.S.P.	12.60
2	Methocel 60 HG.—50 viscosity	509.20
3	Methyl paraben U.S.P.	0.52
4	Propyl paraben U.S.P.	0.06
5	Syloid 244 (Silica aerogel)	2.63

Ingredient 2 was placed in a suitable bowl or container and ingredients 1, 3, 4 and 5 were weighed out and added after screening and the whole blended for 20 minutes following which the compression into tablets took place on a tableting machine using a die size of 7/16" with a punch of 7/16" to obtain a tablet thickness of 0.250 ± 0.01" with a tablet hardness of 11—13 kg/square inch. Each tablet weighed 0.525 g.

EXAMPLE IV
Appetite Satient

	Ingredients	mg/tablet
1	Methocel 60 HG.—50 viscosity	60.0
2	Benzocaine	9.9
3	Saccharin	0.3
4	Felcofix peppermint	1.5
5	Felcofix cherry flavor No. 1265	2.5
6	Carbowax 6000W	0.4
7	Syloid 244 (Silica aerogel)	0.4
8	Methyl paraben U.S.P.	0.075
9	Propyl paraben U.S.P.	0.0075

Ingredient 1 was placed in a stainless steel bowl as in the previous examples and ingredients 2—9 were also weighed out and screened and all ingredients thoroughly mixed and blended in a bowl for 20 minutes following which they were compressed into tablets on a tableting machine having a die size of 7/32" and a punch of 7/32" to form tablets having a thickness of 0.110" and a hardness of 7—10 kg/square inch. Each tablet weighed 0.075 g.

EXAMPLE V
Laxative

	Ingredients	mg/tablet
1	Phenolphthalein U.S.P.	33.0
2	Methocel 60 HG.—50 viscosity	513.64
3	Methyl paraben U.S.P.	0.55
4	Propyl paraben U.S.P.	0.06
5	Syloid 244 (Silica aerogel)	2.75

Ingredients 1 and 2 were placed in a stainless steel bowl to which after screening were added ingredients 3, 4 and 5 and the whole blended for 20 minutes and compressed as in Example III. The tablet thickness was 0.250" ± 0.01" and the hardness was 10 kg/square inch. Each tablet weighed 0.55 g.

EXAMPLE VI
Laxative

	Ingredients	mg/tablet
1	Phenolphthalein U.S.P.	66.0
2	Methocel 60 HG.—50 viscosity	480.64
3	Methyl paraben U.S.P.	0.55
4	Propyl paraben U.S.P.	0.06
5	Syloid 244 (Silica aerogel)	2.75

The same procedure was followed as in Example V with the same results.

EXAMPLE VII
Breath Wafers

	Ingredients	mg/tablet
1	Cerelose (Dextrose—fine granules)*	629.9
2	Sorbitol	37.5
3	Mannitol	37.5
4	Sodium bicarbonate U.S.P. granular	15.0
5	Stearic acid	15.0
6	Syloid 244 (Silica aerogel)	7.5
7	Oil of peppermint U.S.P.	3.8
8	Oil of wintergreen U.S.P.	3.8

*(The word "Cerelose" is a Registered Trade Mark).

Ingredients 1—5 were placed in a stainless steel bowl, ingredients 7 and 8 were adsorbed on ingredient 6 and screened and added to the stainless steel bowl. All ingredients were mixed and blended for 20 minutes and compressed as previously described except that the tablets were in wafer form with a thickness of 0.175" ± 0.01" with a hardness of 8—10 kg/square inch. Each tablet weighed 0.75 g.

EXAMPLE VIII
Decongestant

	Ingredients	mg/tablet
1	Cerelose (Dextrose—fine granular)	728.5
2	Sorbitol	42.5
3	Mannitol	42.5
4	Stearic acid	17.2
5	Menthol	4.3
6	Oil of Eucalyptol	2.1
7	Camphor	4.3
8	Syloid 244 (Silica aerogel)	8.6

Ingredients 1—4 were screened and placed in a stainless steel bowl, ingredients 5, 6 and 7 were triturated until they became liquid and then adsorbed on ingredient 8. The mixture was screened into the other ingredients which had already been placed into the stainless steel bowl and blended and compressed as previously described. The tablets had a thickness of 0.200" ± 0.01" and a hardness of 8—10 kg/square inch. Each tablet weighed 0.85 g.

EXAMPLE IX
Vitamin

	Ingredients	mg/tablet
1	Ascorbic acid U.S.P. powder	105
2	Methocel 60 HG.—50 viscosity	691
3	Syloid 244 (Silica aerogel)	4

Ingredients 1 and 2 were weighed out as in the preceding examples and placed into a stainless steel bowl into which ingredient 3 was added after screening and the whole blended for 20 minutes and compressed as previously described. The tablets had a thickness of 0.210" ± 0.01" and a hardness of 11—13 kg/square inch. Each tablet weighed 0.8 g.

The release pattern of active ingredient from the new long lasting oral carrier can be varied according to the particular type of medication and its intended mode of administration. For a sublingual lozenge or tablet the release pattern varies from about 1/4 hour to 2 hours and this is at least in part controlled by the size and degree of compression used in forming the lozenge or tablet since larger tablets last longer and higher compressions give a slower rate of release. For oral tablets which are swallowed the rate of release is usually 8 to 10 hours and this has been confirmed by X-rays with barium sulfate to show the motility and disintegration in the intestinal tract. For vaginal and rectal suppositories the release pattern ranges from 12 to 36 hours although it can of course be less where indicated. By predetermining the size of the lozenge or tablet and the amount of compression employed in shaping it from the powder form and by keeping the end product moisture content between 0.7 and 1.0%, predetermined release patterns of reliable and constant characteristics can be secured. This is often very important medically, especially when treating patients having coronary diseases as with nitroglycerin, or related problems of circulatory disorders or abnormal blood pressure. The invention is particularly important also in treating such conditions as ulcerated tissue or mucous lesions and other conditions arising from local hyperacidity or metabolic dysfunction in the physiological system. The invention is therefore of very versatile and adaptable nature giving it a wide scope of application and use.

The foregoing Examples 1 to 6 and 9 are examplary of compositions and products responding to the present invention, but it is to be understood that they are illustrative and not limitative since many active ingredients of various types can be employed in the new long-lasting oral carrier so long as they are absorbable through buccal tissue and the general intestinal tract. The invention is also intended to cover other dosage forms or forms for application of sustained release ingredients such as vaginal and rectal suppositories. The lozenges and tablets particularly act on oral, oropharyngeal and pharyngeal regions. The total dosage is governed by usual medical considerations or physicians' directions and when sufficiently large doses of active agent are incorporated in the lozenges and tablets systemic as well as local action is obtained.

WHAT I CLAIM IS:—

1. A shaped and compressed pharmaceutical composition, which composition comprises a pharmaceutically active ingredient incorporated in a carrier material which is hydroxypropyl methylcellulose or a mixture of hydroxypropyl methylcellulose and sodium carboxymethylcellulose, the carrier material having been humidity and heat treated at a temperature between 110 and 120°F treated at a humidity of 85 to 90% for a minimum of 24 hours and the carrier and pharmaceutically active ingredient having been compressed into shape at a pressure of from 7 to 13 kg/square inch, characterised by a long lasting slow disintegration rate to give the prolonged and regular release pattern.

2. A composition as claimed in Claim 1, wherein the moisture content of the carrier material is between 0.7 and 1% by weight.

3. A composition as claimed in Claim 1 or 2, wherein the active ingredient is a buccally absorbable active ingredient.

4. A composition as claimed in any of Claims 1 to 3, wherein the composition contains 0 to 20% ethyl cellulose, by weight.

5. A composition as claimed in any of Claims 1 to 4, wherein the active ingredient acts transmucosally through the buccal tissues of the mouth when in lozenge form and through other body tissues when in tablet or suppository form.

6. A composition as claimed in any of Claims 1 to 5, in compressed lozenge sublingual form in which the active ingredient is selected from gastric mucin, aluminium hydroxide, magnesium trisilicate, nitroglycerin, amyl nitrite, 1 - ascorbic acid, chlorpheniramine maleate, benzocaine, phenolphthalein and dextrose, or mixtures thereof.

7. A composition as claimed in any of Claims 1 to 6 shaped into lozenge form and which contains an effective amount of an active ingredient which is released regularly and minimally over a period of time related to the size of the tablet and the degree of its compression.

8. A compressed lozenge as claimed in Claim 7, in which the carrier material and the active ingredient constitute at least 80 to 90% of the weight.

9. A composition as claimed in Claim 7 or 8, wherein the release time of the active ingredient ranges from 1/4 to 2 hours for sublingual use.

10. A composition as claimed in Claim 1 substantially as described with reference to Examples 1 to 6 and 9.

11. A method of producing a lozenge or tablet containing a pharmaceutically active ingredient effective over a predetermined period of time related to the size and degree of compression of the lozenge or tablet, which method comprises humidity and heat treating a carrier comprising hydroxypropyl methylcellulose at a temperature between 110 and 120°F at a humidity of 85 to 90% for a minimum of 24 hours, mixing the humidity treated carrier with the active ingredient in

powder form and compressing them at a pressure of 7 to 13 kg/square inch.

12. A method according to claim 11 in which sodium carboxymethylcellulose and 0 to 20% by weight of ethyl cellulose are mixed with the hydroxypropyl methylcellulose.

13. A method as claimed in Claim 11 substantially as described with reference to Examples 1 to 6 and 9.

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